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Solid-Vapor Interactions: Influence of Environmental Conditions on the Dehydration of Carbamazepine Dihydrate

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ABSTRACT

The goal of this research was a phenomenological study of the effect of environmental factors on the dehydration behavior of carbamazepine dihydrate. Dehydration experiments were performed in an automated vapor sorption apparatus under a variety of conditions, and weight loss was monitored as a function of time. In addition to lattice water, carbamazepine dihydrate contained a significant amount of physically bound water. Based on the kinetics of water loss, it was possible to differentiate between the removal of physically bound water and the lattice water. The activation energy for the 2 processes was 44 and 88 kJ/mol, respectively. As expected, the dehydration rate of carbamazepine dihydrate decreased with an increase in water vapor pressure. While dehydration at 0% relative humidity (RH) resulted in an amorphous anhydrate, the crystallinity of the anhydrate increased as a function of the RH of dehydration. A method was developed for in situ crystallinity determination of the anhydrate formed. Dehydration in the presence of the ethanol vapor was a 2-step process, and the fraction dehydrated at each step was a function of the ethanol vapor pressure. We hypothesize the formation of an intermediate lower hydrate phase with unknown water stoichiometry. An increase in the ethanol vapor pressure first led to a decrease in the dehydration rate followed by an increase. In summary, the dehydration behavior of carbamazepine dihydrate was evaluated at different vapor pressures of water and ethanol. Using the water sorption apparatus, it was possible to (1) differentiate between the removal of physically bound and lattice water, and (2) develop a method for quantifying, in situ, the crystallinity of the product (anhydrate) phase.

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INTRODUCTION

The solid state of the active pharmaceutical ingredient may influence the pharmaceutically relevant physicochemical properties including the dissolution rate, flowability, compressibility, and stability (both physical and chemical). Conventionally, material characterization studies are restricted to the raw materials. Phase transitions may occur during the various processing steps involved in the preparation of a pharmaceutical formulation (ie, milling, granulation, drying, and compaction) and also at the time of storage. In recent years, there has been an increased regulatory interest to characterize and to control the physical form of active pharmaceutical ingredients in dosage forms.[1]

In pharmaceutical materials, phase transitions are often mediated by water. Water can associate with solids in a variety of ways. In case of hydrates, water is usually incorporated in the lattice in stoichiometric proportions. Water may also be adsorbed on the solid surface or sorbed in the disordered regions of the lattice. In the latter case, the amount of water held is variable and depends on the method of preparation of the solid and storage conditions.

Distinguishing between the different states of water in solids is an analytical challenge. There are 2 commonly used methods for determination of water content in solids—Karl Fischer titrimetry and thermogravimetry. Both these methods are suitable to quantify the total water in a sample and do not readily distinguish between sorbed (physically bound) and lattice water. The water-solid interaction is expected to be much stronger when water exists in the crystal lattice in stoichiometric proportions, rather then in a sorbed state. If water removal is performed under carefully controlled conditions, it might be possible to differentiate between the physically bound and lattice water in a crystalline solid. Moreover, the activation energy for water removal is expected to be different for the 2 cases.

Carbamazepine ($C_{15}H_{12}N_2O$), 5H-dibenz[b, *f*]azepine-5-carboxamide, a drug used in the treatment of epilepsy and trigeminal neuralgia was the model compound. In addition to several polymorphic forms of anhydrous carbamazepine, a dihydrate and acetone solvate have also been reported.[2-8]

Dehydration of carbamazepine dihydrate has interesting consequences. Dehydration under low water vapor pressure results in an amorphous anhydrate, whereas high vapor pressure results in crystalline γ-carbamazepine.[2] Amorphous anhydrous carbamazepine is unstable at ambient temperatures and readily crystallizes following <1% wt/wt water uptake.[4] This behavior is puzzling in light of its hydrophobic nature. Any process that delays the removal of water (eg, dehydration under high water vapor pressure) should lead to the crystallization of the amorphous anhydrate formed during dehydration. Likewise, a process that increases the dehydration rate may ensure the formation of amorphous anhydrate. Thus, the temperature and composition of vapor during desolvation govern the solid state of the final product. It is well established that organic solvents facilitate the dehydration process.[9-12] The presence of water vapor is known to have a similar effect on desolvation of organic solvates. Pikal et al have shown that the desolvation rate of cefamandole sodium methanolate could be dramatically increased in the presence of water vapor.[13]

The goal of this research was a phenomenological study of the effect of various environmental factors on the dehydration behavior of carbamazepine dihydrate. The specific objectives include, (1) differentiating between physically bound and lattice water, (2) in situ solid-state characterization of the phase obtained after dehydration under a variety of conditions, and (3) evaluating the dehydration kinetics in presence of water and ethanol vapor. An automated vapor sorption balance and vapor pressure controlled x-ray powder diffractometry were the main characterization tools.

MATERIALS AND METHODS

Crystalline carbamazepine anhydrate ($C_{15}H_{12}N_2O$, Sigma, St Louis, MO) was used as obtained. The dihydrate was prepared by dispersing the crystalline anhydrate in water for 24 hours. It was then filtered and stored at 98% relative humidity (RH) (over saturated solution of $CuSO_4 \cdot 5H_2O$) at room temperature for ~12 hours. These samples were packed in small vials to prevent removal of sorbed water and stored at ~79% RH (over saturated solution of NH_4Cl) at room temperature.

Experimental

Automated Vapor Sorption Balance

About 6-10 mg of wet carbamazepine dihydrate powder was placed in the sample pan of the vapor sorption balance (DVS-1000, Surface Measurements Systems, London, UK) and exposed to the solvent vapor. The desired solvent vapor pressure was obtained by mixing appropriate proportions of dry nitrogen with nitrogen saturated with solvent vapor, and the gas flow rate was 200 mL/min. The solvents used were distilled water and absolute ethanol. The experiments were carried out isothermally at 25°C unless otherwise mentioned. The microbalance was calibrated using a 100 mg standard weight. The RH sensor was calibrated at 5.0, 11.3, 32.8, 52.8, 75.3, and 84.3% RH (25°C), using saturated salt solutions.

X-ray Diffractometry

An x-ray powder diffractometer (Model XDS 2000, Scintag, Cupertino, CA) with a variable temperature stage (Model 828D, Micristar, R.G. Hansen and Associates, Santa Barbara, CA) was used to control the sample temperature. Water and organic vapor pressure control was achieved using a previously described assembly,[14] wherein a flow rate of 200 mL/min was used. About 50 mg of the sample was filled in the holder and exposed to Cu Kα radiation (45 kV × 40 mA) in the continuous mode at chopper increments of 0.05°2θ. The angular range was 5°2θ to 40°2θ, and the scanning rate was 3°2θ/min. During the x-ray diffractometry (XRD) run, the sample was maintained under isothermal conditions. A small sample size of about 10 mg was used for the in situ study of dehydration behavior. This was done to enable a meaningful comparison with vapor sorption results where the sample size is small. Unless otherwise stated, all experiments were performed isothermally at 25°C.

Thermal Analysis

A differential scanning calorimeter (MDSC, Model 2920, TA Instruments, New Castle, DE) with a refrigerated cooling accessory was used. The instrument was calibrated with pure samples of tin and indium. Depending upon the information sought, the samples (4-8 mg) were analyzed either in open or in crimped aluminum pans under dry nitrogen purge at a heating rate of 10°C/min.

RESULTS AND DISCUSSION

Characterization of the Starting Materials

Carbamazepine obtained from the commercial supplier was identified to be the anhydrous β- polymorph, which is con-

sidered to be the stable form under ambient conditions.[5,15,16] The XRD pattern of the prepared carbamazepine dihydrate was in excellent agreement with the published powder pattern.[15] The water content of this incompletely dried solid was ~30% wt/wt, which was significantly higher than the stoichiometeric water content of the dihydrate (13.2% wt/wt). Most of the particles were <100 μm in size.

When carbamazepine dihydrate was heated at 10°C/min in an open pan, 2 endotherms were observed. The first one encompassed dehydration and vaporization of water, and the second was due to the melting of the anhydrate. When carbamazepine dihydrate was dried at 30°C for an hour in an open pan, amorphous anhydrous carbamazepine was formed. This amorphous phase was characterized by a glass transition (onset at ~56°C), followed by a crystallization exotherm at ~85°C, and an endotherm due to melting of the crystalline phase at 188°C (γ-carbamazepine). These results were in good agreement with the earlier results from our laboratory.[4]

Effect of Temperature on Dehydration Behavior of Carbamazepine Dihydrate

Carbamazepine dihydrate (incompletely dried) was subjected to isothermal dehydration under nitrogen purge (0% RH) in the vapor sorption balance at temperatures ranging from 17°C to 40°C. **Figure 1A** is a representative plot of change in sample weight as a function of time. The weight loss occurred in 2 stages. Rapid loss was observed in the first stage, and the linear profile indicated zero order kinetics. The weight loss was slower in the second stage, and there was a distinct change in slope of the profile at the intersection of the 2 stages. The loss in the first stage was variable, but the second-stage weight loss was almost constant (13.2% ± 0.1%; n > 15), which matched the stoichiometric water content of carbamazepine dihydrate (13.2% wt/wt). Thus, the second stage can be attributed to the dehydration of carbamazepine dihydrate (ie, removal of lattice water). The first stage was the release of physically bound (ie, sorbed) water. The material obtained after the second-stage weight loss was completely dry and did not contain any sorbed water. Since the total water content of incompletely dried carbamazepine dihydrate was variable, all the results are plotted based on the weight of the dry sample obtained after complete dehydration. Thus, the weight of the anhydrate phase obtained following dehydration was considered as 100%, and all other sample weights were adjusted accordingly.

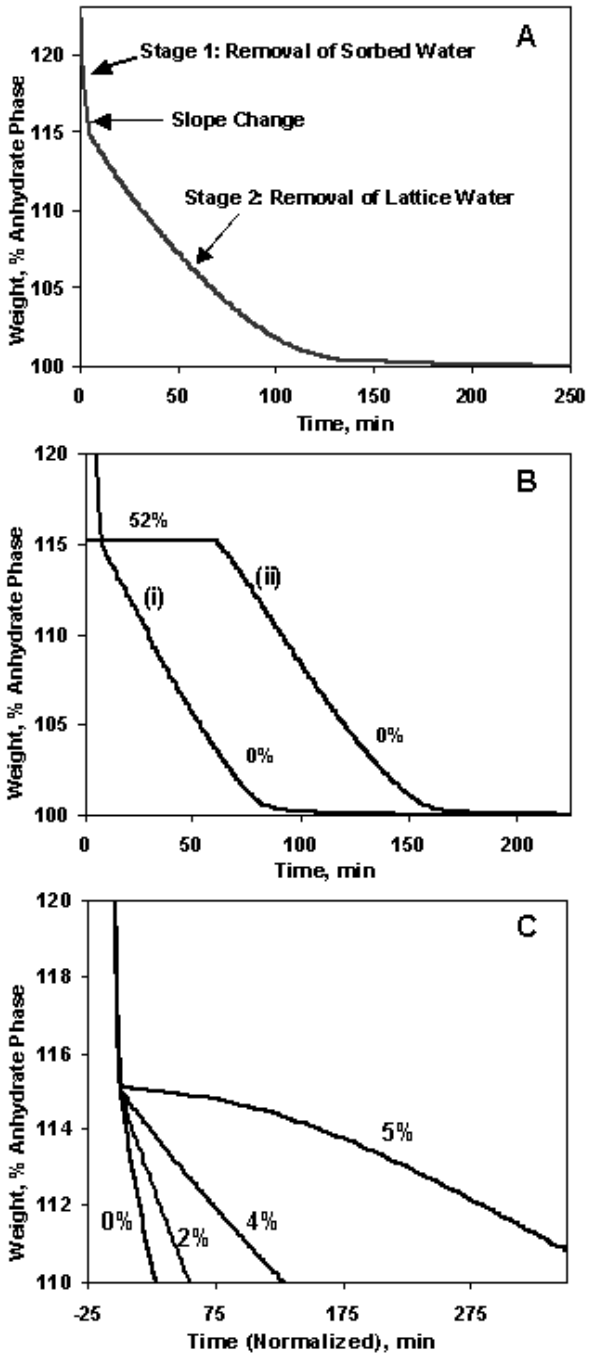

Figure 1. Dehydration of carbamazepine dihydrate studied under a variety of conditions at 25°C. The plotted sample weight is based on the dry sample weight after complete dehydration (details in text). (A) Dehydration of the wet sample at 0% RH. The first and second stages of dehydration are separated by the point of slope change. (B) Overlaid dehydration profiles of carbamazepine dihydrate at 0% RH, (i) without and (ii) after prior storage at 52% RH. (C) Overlaid dehydration patterns following exposure to RH values ranging from 0% to 5%. For the purpose of comparison, the x-axis has been normalized for the beginning of stage 2.

In order to prove that the second step was indeed the removal of lattice water, 2 approaches were taken. In the first case, carbamazepine dihydrate was exposed to 52% RH in the vapor sorption balance for an extended time period followed by exposure to 0% RH (dry nitrogen flow). This procedure was based on previous studies[2,4] that have shown that carbamazepine dihydrate was stable at 52% RH at room temperature and contained a negligible amount of sorbed water. The dehydration profile following this treatment was compared with the one obtained by direct exposure to 0% RH (**Figure 1B**). From the plot, it is clear that the second stage of the weight-loss profile of the first sample (exposed directly to 0% RH) is identical to that of the second sample (equilibrated at 52% RH followed by exposure to 0%). The weight loss in both the cases was about 13.2%, and both had identical dehydration kinetics. In the second approach, dehydration kinetics at 4 water vapor pressures (ie, 0, 2, 4, and 5% RH) were compared (**Figure 1C**). With a small increase in vapor pressure (0% → 5% RH), there was a considerable change in the rate of second-stage weight loss, while that of the first stage remained virtually unaffected. As can be expected, a small change in RH did not have an appreciable effect on the removal of loosely bound water, but the elimination of lattice water was dramatically affected. The above comparison clearly shows that the second step was indeed the loss of lattice water, while the sorbed water was lost in the first step.

Thus, the vapor-sorption balance was able to differentiate between the physically bound water and the lattice water. The differentiation was possible because of the 2-stage weight loss—complete loss of sorbed water followed by the loss of lattice water (dehydration). Many hydrates, when exposed to ambient conditions, even for a short time period, tend to undergo partial dehydration. Unambiguous characterization of such hydrates becomes difficult if they undergo dehydration during sample preparation. The ability to differentiate between the solvent present in the lattice and in the bulk not only helps in characterization of different states of solvent in a material but may also be instrumental in the unambiguous characterization of solvates.

The next objective was to study the temperature dependence of dehydration and desorption processes and determine their activation energy values. The desorption and dehydration data at temperatures ranging from 17°C to 40°C (**Figures 2A** and **B**), were fitted to various solid-state kinetic model equations. The removal of physically bound water was found to be a zero-order process. The dehydration process (**Figure 2B**) was best described by the 2-dimensional phase boundary controlled kinetics. These conclusions were based on the value of the correlation coefficient, *r*, obtained after data fitting. It is recognized that fitting of data alone cannot form the basis for deducing the reaction mechanism. However, the kinetic analysis is a good starting point for understanding the reaction mechanism.

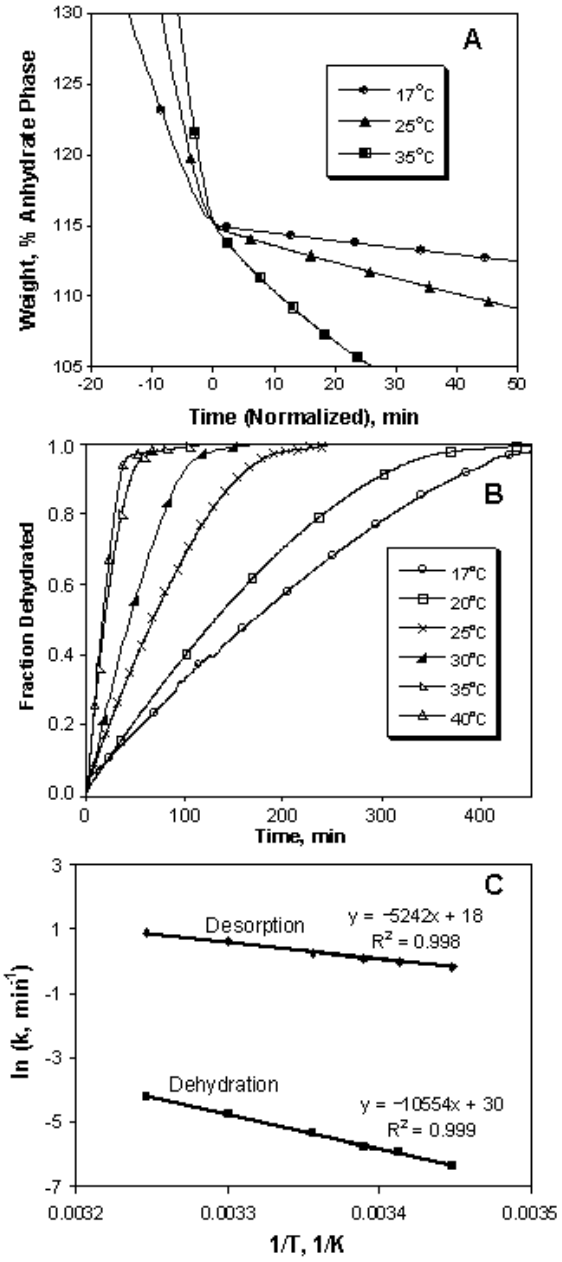

Figure 2. Effect of temperature on desorption and dehydration kinetics of carbamazepine dihydrate. (A) Desorption and dehydration profiles at 3 representative temperatures. For the purpose of comparison, the x-axis origin is the time point of transition from desorption to dehydration (point of slope change in Figure 1A). (B) Kinetics of dehydration as a function of temperature. The temperature ranged from 17°C to 40°C. (C) Arrhenius plot for desorption and dehydration reactions, wherein the rate constant (natural logarithmic scale) was plotted as a function of the inverse of experimental temperature ($n \geq 3$).

The activation energy for the 2 processes was determined from the Arrhenius plot (**Figure 2C**). The activation energies for desorption and dehydration were 44 kJ/mol and 88 kJ/mol, respectively. In an earlier investigation, the activation energy for dehydration, determined from the study of dehydration kinetics by thermogravimetric analysis, was calculated to be 68.8 kJ/mol.[2] This discrepancy is possibly due to differences in experimental conditions, including sample size, geometry, and gas flow rate.

The association of water in pharmaceutical solids has been a subject of intense interest.[17] Based on the kinetics of water loss, we were able to readily distinguish between physically bound and lattice water in crystalline carbamazepine dihydrate. It was also possible to quantify the water in these 2 states. Since the physically bound water is much more "mobile" than the lattice water, it can facilitate and participate in physical and chemical transformations.

Effect of Water Vapor Pressure on the Solid State of the Phase Obtained After Dehydration

As discussed earlier, the environmental vapor pressure during dehydration can affect the solid state of the anhydrate phase formed. Thus, the next objective was to study the effect of water vapor pressure during dehydration on the crystallinity of the dehydrated phase. From this point on, the interest was solely in the second stage of weight loss (ie, the dehydration of the hydrate). The dehydration kinetics (at 44ºC) of carbamazepine dihydrate at water vapor pressures ≤5.1 torr was best described by the 2-dimensional phase boundary controlled model, whereas at vapor pressures ≥12.0 torr, the 3-dimensional nucleation and growth model was best.[2] At an intermediate vapor pressure of 7.6 torr, it was not possible to model the data. From humidity-controlled XRD results, it was shown that at low vapor pressures, dehydration resulted in an amorphous anhydrate, while at high vapor pressures, the crystalline anhydrate was formed.[2] Since the kinetics of dehydration was studied in a thermogravimetric analyzer (TGA), it was not possible to evaluate the solid state (in terms of the degree of crystallinity) of the product phase.

Carbamazepine dihydrate was dehydrated at several RH values ranging from 0% to 5% (**Figure 3A**). As expected, an increase in water vapor pressure decreased the rate of dehydration. Irrespective of the water vapor pressure, the data could be best fitted to the 2-dimensional phase boundary controlled model. It was earlier observed that, when the dehydration was phase boundary controlled, the product phase was amorphous anhydrate.[2] It is recognized that the reaction mechanism alone cannot form the basis for deducing the solid state of the final product. Even if the dehydration resulted in an amorphous anhydrate, crystallization could then follow. From **Figure 3A** it is clear that as the RH was increased, retention of water in the sample was favored, which could then facilitate crystallization of the anhydrate.

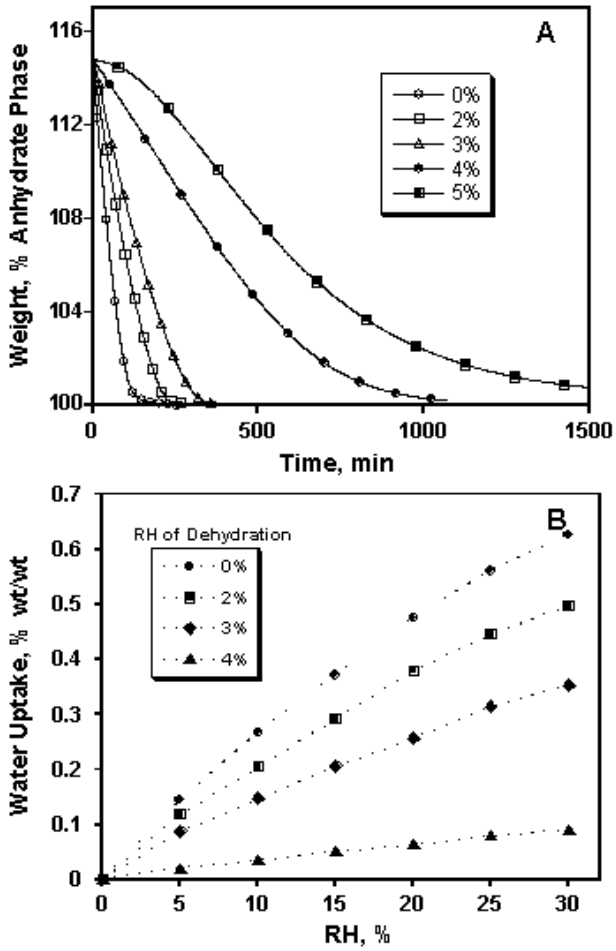

Figure 3. (A) Effect of water vapor pressure on the kinetics of dehydration of carbamazepine dihydrate at 25°C. (B) Water uptake of anhydrous carbamazepine (obtained in [A]) as a function of RH at 25°C. Dehydration was performed at RH values ranging from 0% to 5%, while vapor sorption was studied in the RH range of 0% to 30%.

X-ray diffractometry of the dehydrated product revealed that crystallization had occurred during the drying (results not shown). Moreover, the degree of crystallinity of the anhydrate increased with an increase in the water vapor pressure (2% → 5% RH).

Degree of Crystallinity of the Dehydrated Phase—In Situ Quantification

Our next interest was to quantify, in situ, the degree of crystallinity of the anhydrate phase formed after dehydration under different RH conditions (**Figure 3A**). The degree of crystallinity of an unknown sample is usually expressed

Table 1. The Effect of Water Vapor Pressure During Dehydration (25°C) on the Degree of Crystallinity of the Anhydrous Carbamazepine

RH* of Dehydration	Percentage Amorphous Carbamazepine
2%	79.4 (1.7)
3%	56.2 (2.2)
4%	14.1 (0.6)

*RH indicates relative humidity. The results presented are in terms of the amorphous phase concentration in the mixture: mean (SD); n = 6.

with reference to well-characterized crystalline and amorphous standards. The "as is" carbamazepine (β-polymorph) sorbed negligible amount of water in the RH range of 0% to 40% and was considered as the crystalline standard. The anhydrate prepared by dehydration of carbamazepine dihydrate at 0% RH was x-ray amorphous and was considered as the amorphous standard.

The anhydrate samples obtained after dehydration under different RH conditions (**Figure 3A**) were exposed to RH values ranging from 5% to 30%, at 5% RH increments, and the water uptake was measured (**Figure 3B**). The degree of crystallinity (in terms of the percentage of amorphous phase) was determined using Equation 1.

$$\% \text{ Amorphous Carbamazepine} = \left(\frac{\% \text{ wt/wt water sorbed by the sample}}{\% \text{ wt/wt water sorbed by the reference material}} \right) \times 100 \quad (1)$$

Since the water sorption was quantified at 6 RH values, 6 crystallinity values were obtained for each sample (**Table 1**). As the RH during dehydration increased, the crystallinity of the anhydrate increased. At RH ≥5%, the anhydrate formed was completely crystalline and did not sorb any water. It is significant that small changes in the water vapor pressure during dehydration had a very pronounced effect on the crystallinity of the anhydrous phase obtained. Thus, a change in the RH (at 25°C) of dehydration from 0% to 4% caused an increase in the percentage crystallinity of the anhydrate from 0% to 86%. These results demonstrate that careful control of the dehydration conditions is necessary in order to maintain consistency in the physical form of the anhydrate.

It should be noted that the effect of water vapor pressure *during* dehydration was different from that after the formation of the amorphous anhydrate. While an RH ≥5% during dehydration caused complete crystallization of the anhydrate phase, the amorphous anhydrate (formed after dehydration at 0% RH) once formed did not crystallize when exposed to RH values up to 30% (**Figure 3B**). This finding was further confirmed when selected samples were exposed to RH values ranging from 5% to 30% for prolonged periods of time and there was no evidence of crystallization.

Conventional crystallinity determination requires preparation of samples of known degree of crystallinity by mixing crystalline and amorphous reference standards.[18] In addition to the challenges in the selection of these standards, preparation of homogeneous mixtures is very difficult when the degree of crystallinity is very high (>90%) or very low (<10%). The proposed method does not require the generation of a standard curve. Moreover, water vapor sorption is considered to be a very sensitive indicator of lattice disorder.[19] However, it is now recognized that thermal history can influence both the rate and extent of water uptake by amorphous pharmaceuticals.[20] In our systems, the thermal history is not a variable since all the samples were prepared in situ by the same method.

The state of a partially crystalline material has been described using a 1-state and a 2-state model.[18] In the 2-state model, there are distinct amorphous and crystalline regions as will be observed in physical mixtures of the amorphous and crystalline standards. On the other hand, the 1-state model does not assume distinct boundaries between the 2 phases. When amorphization occurs during pharmaceutical unit operations, usually the latter model is more realistic. Often, the crystallinity determination methods rely on generation of a standard curve using a mixture of the amorphous and crystalline standards (thus utilizing the 2-state model). An ideal degree of crystallinity determination method would be one in which the sample and standard preparation methods were identical. The method detailed in this work satisfies this requirement.

Effect of Ethanol Vapor Pressure on Dehydration of Carbamazepine Dihydrate

Since ethanol is a granulating agent, it was of interest to study the effect of ethanol vapor pressure on the dehydration of carbamazepine dihydrate. All the experiments were performed at 25°C, at which temperature the saturated ethanol vapor pressure (p_o) is 59.77 torr.[21] Dehydration was studied at ethanol vapor pressures of 1.2, 1.8, 3.0, 4.2, 6.0, 9.0, 14.9, 23.9, and 35.9 torr (p/p_o = of 0.02, 0.03, 0.05, 0.07, 0.10, 0.15, 0.25, 0.40, and 0.60, respectively). In each case, after dehydration, the samples were dried under nitrogen purge to remove any sorbed ethanol. This was particularly important because of the high solubility of carbamazepine in ethanol.

Moreover, this step was necessary to unambiguously determine the weight of the anhydrate phase obtained.

The overlaid dehydration profiles, as a function of ethanol vapor pressure, are plotted in **Figure 4**. The dehydration profile under dry nitrogen purge has been provided for comparison. As is evident from the figure, the presence of ethanol vapor had a major impact on the dehydration profiles of carbamazepine dihydrate. In all cases the total weight loss matched the stoichiometric water content of carbamazepine dihydrate (~13.2% wt/wt). The presence of the nonaqueous solvent was expected to accelerate the dehydration of carbamazepine dihydrate. However, dehydration under these conditions was considerably slower (>400 minutes) compared with that observed in absence of ethanol (~200 minutes). This issue is addressed in detail in the subsequent discussion.

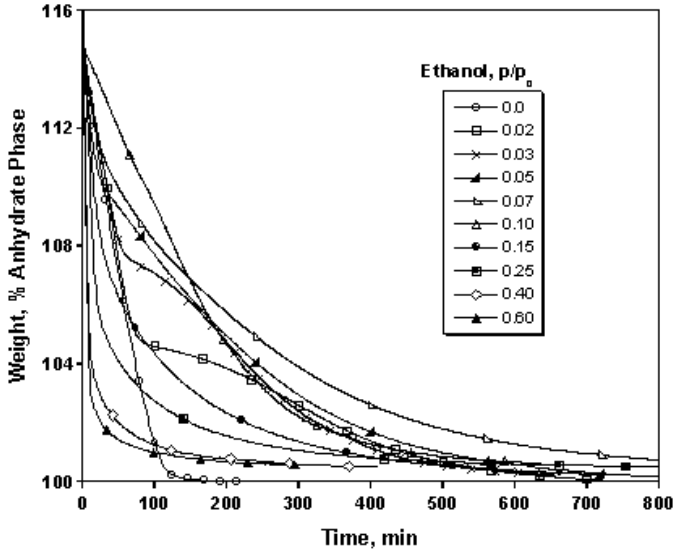

Figure 4. Effect of the vapor pressure of ethanol on dehydration of carbamazepine dihydrate. For comparison, dehydration profile in the absence of ethanol is also shown. Replicate analysis was performed in selected cases. For ease of observation, the SDs are not shown on the plot. However, the coefficient of variation values were typically less than 2% for more than 90% of the data points.

At vapor pressures ≤4.2 torr ($p/p_o \leq 0.07$), the dehydration profiles appear to be characterized by 2 steps (**Figure 4**). The rapid first step coincided with the dehydration rate in the absence of ethanol and was not affected appreciably by ethanol vapor pressure. The second step, on the other hand, was slower, wherein the rate increased with ethanol vapor pressure. The data from the individual steps were fitted to various solid-state models. The first step was best described by the 2-dimensional phase boundary controlled model, while the 3-dimensional nucleation-controlled kinetics provided the best fit for the second step (data not shown). We had previously observed that when the kinetics of dehydration was phase boundary controlled, the product was amorphous anhydrate, while nucleation-controlled kinetics resulted in crystalline anhydrate.[2] Thus, the 2 steps observed here possibly signify the formation of, first amorphous, followed by crystalline carbamazepine phases. The higher the vapor pressure ($p/p_o \leq 0.07$), the faster was the recrystallization and the shorter was the first step. In presence of ethanol vapor, the dehydrated (amorphous) phase experienced the combined plasticizing effect of water (Tg_{water} = 135 K) liberated by dehydration as well as ethanol ($Tg_{ethanol}$ = 96 K). The plasticizing effect is expected to become more pronounced with an increase in the vapor pressure of ethanol.

The XRD and differential scanning calorimetry (DSC) analysis showed that the phase obtained after dehydration was highly crystalline (mixture of β- and γ-carbamazepine). Thus, the outstanding questions were as follows: (1) If the amorphous phase is formed during dehydration, why is it not seen in the final product? (2) Moreover, why is there a change in the reaction mechanism? One possible explanation is that at lower vapor pressures (1.2 to 4.2 torr), dehydration results in amorphous anhydrate, which subsequently crystallizes due to the plasticizing effect of ethanol. With an increase in the crystalline phase content, further dehydration results in direct formation of the crystalline anhydrate. The early onset of the second step, with increase in vapor pressure (rapid crystallization of the amorphous anhydrate formed in the process), provides a strong support for this theory. This may also explain why the ethanol vapor pressure also has a stronger effect on the second step of the dehydration process than the first step. Nonaqueous solvents accelerated the dehydration process in systems where both the reactant and the product were crystalline.[9-12] In addition, as long as the dehydration resulted in a crystalline anhydrate, the rate of dehydration increased with ethanol vapor pressure.

When the vapor pressure was ≥6.0 torr ($p/p_o = 0.1$), the "first step" (early stage of dehydration, where dehydration led to formation of amorphous anhydrate) disappeared completely. Moreover, the dehydration kinetics was 3-dimensional nucleation controlled. However, in these cases, the dehydration rate slowed down considerably in the end, and it was not possible to model the complete reaction.

At all vapor pressures, based on XRD and DSC analysis, the dehydrated phase was determined to be a mixture of β- and γ-carbamazepine. The β-polymorph content increased with an increase in the ethanol vapor pressure. In order to obtain a mechanistic understanding of the process, dehydration in presence of ethanol vapor was further investigated in an x-ray diffractometer, where the vapor pressure in the sample chamber was controlled. The dehydration behavior of carbamazepine dihydrate was investigated at ethanol vapor

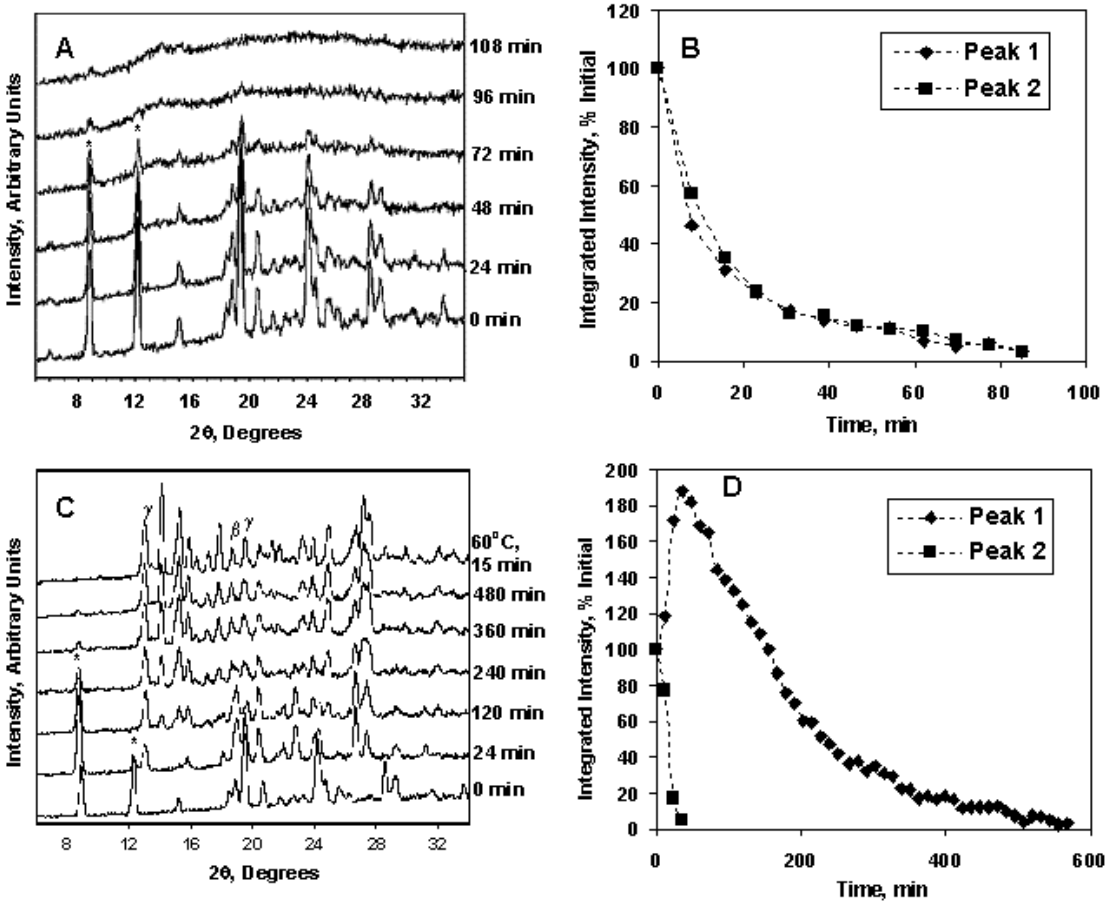

Figure 5. Dehydration of carbamazepine dihydrate in the presence and absence of ethanol vapor. XRD patterns and integrated peak intensities are shown as a function of time. (A) and (B) at 0 torr; (C) and (D) at 4.2 torr. Peak 1 is 8.9°2θ and Peak 2 is 12.3°2θ. Characteristic peaks: carbamazepine dihydrate (*); β-carbamazepine (β); γ-carbamazepine (γ).

pressures of 0, 3.0, 4.2, 14.9, and 35.9 torr at 25°C (corresponding p/p_o = 0, 0.05, 0.07, 0.25, and 0.60, respectively). In all the cases, after obtaining the XRD pattern under ambient conditions, the sample was exposed to the desired ethanol vapor pressure, and scans were obtained at regular intervals. The characteristic peaks of carbamazepine dihydrate (8.9°2θ and 12.3°2θ) as well as β- (14.2°2θ and 18.7°2θ) and γ-anhydrates (13.1, 13.9, 18.2, and 19.9°2θ) were monitored.

As in the case of the vapor sorption studies, rapid dehydration was observed at p/p_o = 0.0, as is evident from the rapid decrease in the peak intensity over the angular range of 5°2θ to 35°2θ range (**Figure 5A**). The dehydration kinetics was monitored based on the integrated intensity of the characteristic carbamazepine dihydrate peaks at 8.9°2θ and 12.3°2θ (peaks 1 and 2, respectively; **Figure 5B**). The intensity of each peak, as a function of time, was plotted separately, and the 2 profiles were virtually superimposable (**Figure 5B**).

Figures 5C and **5D**, demonstrate the effect of ethanol vapor (4.2 torr, p/p_o = 0.07) on the dehydration kinetics. The low peak intensities coupled with the peak broadening, observed at 24 minutes (**Figure 5C**), signify the presence of an amorphous intermediate at the early stages of dehydration. However, at later time points, there was a progressive increase in sharpness of the peaks, indicating crystallization. There was a difference in the rate of disappearance of the 2 characteristic dihydrate peaks at 8.9°2θ and at 12.3°2θ (**Figure 5D**). The intensity of the peak at 12.3°2θ decreased very rapidly, and the peak was no longer observed at ~48 minutes. However, the intensity of the peak at 8.9°2θ first increased and then decreased slowly. This peak could be observed even after 10 hours and disappeared only after heating the sample to 60°C. The characteristic 13.1°2θ peak of anhydrous γ-carbamazepine appeared at ~12 minutes, and its intensity increased with time (**Figure 6C**). The intensity of this peak plateaued in ~1 hour. This was followed by an increase in the intensity of some other peaks (eg, one at 14.2°2θ, char-

acteristic of β-carbamazepine). On complete dehydration, a mixture of anhydrous β- and γ-carbamazepine was obtained.

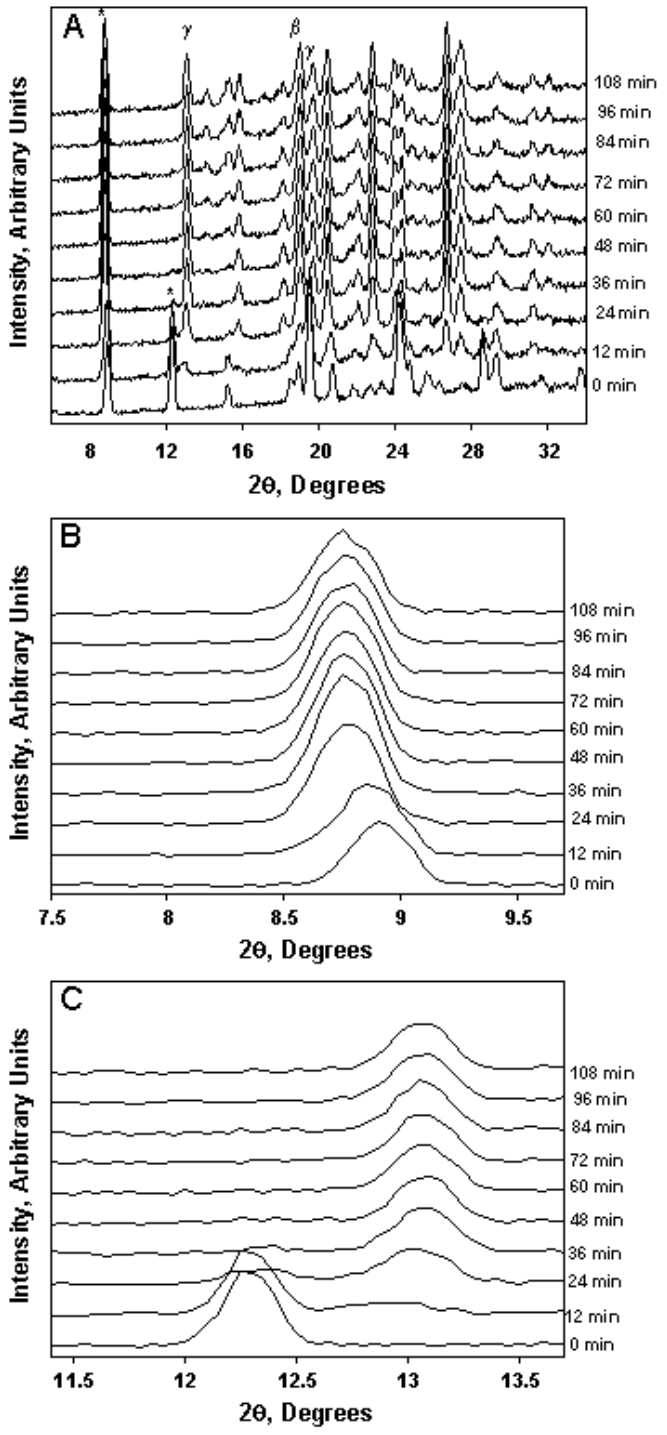

Figure 6. Dehydration of carbamazepine dihydrate at 4.2 torr ethanol vapor pressure. Overlaid XRD patterns from 0 to 108 minutes in the angular range of (A)5°2θ to 35°2θ, (B)7.5°2θ to 9.7°2θ, and (C)11.5°2θ to 13.7°2θ. Characteristic peaks: carbamazepine dihydrate (*); β-carbamazepine (β); γ-carbamazepine (γ).

In an effort to understand the structural changes in the lattice during the dehydration reaction, the XRD results were analyzed in detail. **Figure 6A** contains the XRD patterns obtained between 0 and 108 minutes during the initial stages of dehydration at an ethanol pressure of 4.2 torr (p/p_o = 0.07). **Figures 6B** and **6C** contain the expanded XRD pattern over the angular ranges of 7.5°2θ to 9.7°2θ and 11.5°2θ to 13.7°2θ, respectively. As mentioned earlier, the intensity of the carbamazepine dihydrate peak at 8.9°2θ first increased and then decreased. Moreover, the peak maximum progressively shifted to a lower angle of ~8.8°2θ, reflecting an increase in the d-spacing (ie, lattice expansion) of this diffracting plane. Even after exposure for 108 minutes, the peak was discernible (**Figure 6B**), although there was a slight decrease in the intensity. In contrast, the dihydrate peak at 12.3°2θ completely disappeared in 48 minutes (**Figure 6C**), and the 13.1°2θ peak (γ-carbamazepine) had attained maximum intensity. The XRD pattern of the material at 48 minutes did not completely match with any one of the known forms of carbamazepine (3 anhydrous polymorphs and 1 dihydrate). Results from dehydration studies in the vapor sorption balance indicated that, at this time, the material contained a considerable amount of water suggesting that complete dehydration had not occurred. This suggests that the pattern at 48 minutes is of an intermediate hydrate phase, which eventually converts to a mixture of β- and γ-carbamazepine anhydrate. (Unambiguous proof of an intermediate phase will be the presence of peaks at 2θ values, where the 3 anhydrous polymorphs and the dihydrate do not show any peaks. A confirmatory proof will be the absence of peaks at some 2θ values, where the 3 anhydrate phases and the dihydrate have intense peaks. Such unambiguous characterization was not possible because of the numerous overlapping peaks over the angular range of interest.)

CONCLUSION

The loss of sorbed and lattice water in carbamazepine dihydrate could be differentiated using a vapor-sorption balance. The water vapor pressure during dehydration significantly influenced the crystallinity of the resulting anhydrate. In the presence of ethanol vapor, dehydration proceeded via a crystalline intermediate hydrate.

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